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(54) Title: NUCLEIC ACIDS, PROTEINS, AND ANTIBODIES

(57) Abstract: The present invention relates to novel proteins. More specifically, isolated nucleic acid molecules are provided encoding novel polypeptides. Novel polypeptides and antibodies that bind to these polypeptides are provided. Also provided are vectors, host cells, and recombinant and synthetic methods for producing human polynucleotides and/or polypeptides, and antibodies. The invention further relates to diagnostic and therapeutic methods useful for diagnosing, treating, preventing and/or prognosing disorders related to these novel polypeptides. The invention further relates to screening methods for identifying agonists and antagonists of polynucleotides and polypeptides of the invention. The present invention further relates to methods and/or compositions for inhibiting or enhancing the production and function of the polypeptides of the present invention.

Nucleic Acids, Proteins, and Antibodies

This application refers to a "Sequence Listing" that is provided on electronic media in computer readable form pursuant to Administrative Instructions Section 801(a)(i) and as a paper copy. The Sequence Listing forms a part of this description pursuant to Rule 5.2 and Administrative Instructions Sections 801 to 806, and is hereby incorporated in its entirety.

The Sequence Listing is provided as an electronic file (PA131PCTSL..txt, 5,210,863 bytes in size, created on May 18, 2001) on three identical compact discs (CD-R), labeled "COPY 1," "COPY 2," and "CRF." The Sequence Listing complies with Annex C of the Administrative Instructions, and may be viewed, for example, on an IBM-PC machine running the MS-Windows operating system by using the V viewer software, version 2000 (see World Wide Web URL: http://www.fileviewer.com).

Field of the Invention

[0001] The present invention relates to novel proteins. More specifically, isolated nucleic acid molecules are provided encoding novel polypeptides. Novel polypeptides and antibodies that bind to these polypeptides are provided. Also provided are vectors, host cells, and recombinant and synthetic methods for producing human polynucleotides and/or polypeptides, and antibodies. The invention further relates to diagnostic and therapeutic methods useful for diagnosing, treating, preventing and/or prognosing disorders related to these novel polypeptides. The invention further relates to screening methods for identifying agonists and antagonists of polynucleotides and polypeptides of the invention. The present invention further relates to methods and/or compositions for inhibiting or enhancing the production and function of the polypeptides of the present invention.

Background of the Invention

[0002] Protein transport is a quintessential process for both prokaryotic and eukaryotic cells. Transport of an individual protein usually occurs via an amino-terminal signal sequence, which directs, or targets, the protein from its ribosomal assembly site to a particular cellular or extracellular location. Transport may involve any combination of several of the following steps: contact with a chaperone, unfolding, interaction with a receptor and/or a pore complex, addition of energy, and refolding. Moreover, an

extracellular protein may be produced as an inactive precursor. Once the precursor has been exported, removal of the signal sequence by a signal peptidase activates the protein.

Although amino-terminal signal sequences vary substantially, many patterns [0003] and overall properties are shared. Recently, hidden Markov models (HMMs), statistical alternatives to FASTA and Smith Waterman algorithms, have been used to find shared patterns, specifically consensus sequences (Pearson, W.R. and D.J. Lipman PNAS 85:2444-48 (1988); Smith, T.F. and M.S. Waterman J. Mol. Biol. 147:195-97 (1981)). Although they were initially developed to examine speech recognition patterns, HMMs have been used in biology to analyze protein and DNA sequences and to model protein structure (Krogh, A. et al. J. Mol. Biol. 235:1501-31 (1994); Collin, M. et al. Protein Sci. 2:305-14 (1993)). HMMs have a formal probabilistic basis and use position-specific scores for amino acids or nucleotides and for opening and extending an insertion or deletion. The algorithms are quite flexible in that they incorporate information from newly identified sequences to build even more successful patterns. Other methods exist to identify membrane associated proteins. Klein et al. have developed a method ("ALOM", also called as KKD) to detect potential transmembrane segments in polypeptides (Klein, P. et al. Biochim. Biophys. Acta, 815:468 (1985)). It attempts to identify the most probable transmembrane segment from the average hydrophobicity value over a range of amino acid residues. It predicts whether the segment is a transmembrane segment (INTEGRAL) or not (PERIPHERAL) and thus, can suggest membrane association of a polypeptide.

[0004] Some examples of the protein families which are known to be plasma membrane associated are receptors (nuclear, 4 transmembrane, G protein coupled, and tyrosine kinase), cytokines (chemokines), hormones (growth and differentiation factors), neuropeptides and vasomediators, protein kinases, phosphatases, phospholipases, phosphodiesterases, nucleotide cyclases, matrix molecules (adhesion, cadherin, extracellular matrix molecules, integrin, and selectin), seven transmembrane receptors, ion channels (calcium, chloride, potassium, and sodium), proteases, transporter/pumps (amino acid, protein, sugar, metal and vitamin; calcium, phosphate, potassium, and sodium) and regulatory proteins. Descriptions of some of these proteins (seven transmembrane receptors, kinases, matrix proteins, fibronectins, defensins, EF-hand domain containing

proteins, mac/perforin family members, pancreatic hormones, serine carboxypeptidases, tumor necrosis factors (TNFs)) and diseases associated with their dysfunction follow.

Seven transmembrane receptors-

[0005] The seven transmembrane receptors (also known as heptahelical, serpentine, or G protein-coupled receptors) comprise a superfamily of structurally related molecules. Possible relationships among seven transmembrane receptors (7TM receptors) for which amino acid sequence had previously been reported are reviewed in Probst et al., *DNA and Cell Biology*, 11(1):1-20 (1992). Briefly, the 7TM receptors exhibit detectable amino acid sequence similarity and all appear to share a number of structural characteristics including: an extracellular amino terminus; seven predominantly hydrophobic α -helical domains (of about 20-30 amino acids) which are believed to span the cell membrane and are referred to as transmembrane domains TM 1-7; approximately twenty well-conserved amino acids; and a cytoplasmic carboxy terminus.

[0006] Each 7TM receptor is predicted to associate with a particular G protein at the intracellular surface of the plasma membrane. The binding of the receptor to its ligand is thought to result in activation (i.e., the exchange of GTP for GDP on the α-subunit) of the G protein which in turn stimulates specific intracellular signal-transducing enzymes and channels. Thus, the function of each 7TM receptor is to discriminate its specific ligand from the complex extracellular milieu and then to activate G proteins to produce a specific intracellular signal. Transmembrane domain-3 (TM3) is believed to be essential in signal transduction (Cotecchia et al., *Proc. Natl. Acad. Sci.*, USA, 87:2896-2900 (1990)). Other regions may be essential for biological activity as well (Lefkowitz, *Nature*, 265:603-604 (1993)).

[0007] Mutations in the third intracellular loop of one 7TM receptor (the thyrotropin receptor) and in the adjacent sixth transmembrane domain of another 7TM receptor (the luteinizing hormone receptor) have been reported to be the genetic defects responsible for an uncommon form of hyperthyroidism (Parma et al., *Nature*, 365:649-651 (1993) and for familial precocious puberty (Shenker et al., *Nature*, 365:652-654 (1993)), respectively. In both cases the mutations result in constitutive activation of the G protein receptors. Other studies have shown that mutations that prevent the activation of 7TM receptors are responsible for states of hormone resistance which are responsible for diseases such as

congenital nephrogenic diabetes insipidus. See Rosenthal et al., *J. Biol. Chem.*, 268:13030-13033 (1993). Still other studies have shown that several 7TM receptors can function as protooncogenes and be activated by mutational alteration. Sec, for example, Allen et al., *Proc. Natl. Acad. Sci. USA*, 88:11354-11358 (1991) which suggests that spontaneously occurring mutations in some 7TM receptors may alter the normal function of the receptors and result in uncontrolled cell growth associated with human disease states such as neoplasia and atherosclerosis. Therefore, mutations in 7TM receptors may underlie a number of human pathologies.

Kinases-

[0008] The kinases comprise the largest known group of proteins, a superfamily of enzymes with widely varied functions and specificities. Kinases regulate many different cell proliferation, differentiation, and signaling processes by adding phosphate groups to proteins. Receptor mediated extracellular events trigger the transfer of these high energy phosphate groups and activate intracellular signaling cascades. Activation is roughly analogous to the turning on a molecular switch, and in cases where signalling is uncontrolled, may be associated with or produce inflammation and cancer.

[0009] Almost all kinases contain a similar 250-300 amino acid catalytic domain. The N-terminal domain, which contains subdomains I-IV, generally folds into a two-lobed structure which binds and orients the ATP (or GTP) donor molecule. The larger C terminal lobe, which contains subdomains VIA-XI, binds the protein substrate and carries out the transfer of the gamma phosphate from ATP to the hydroxyl group of a serine, threonine, or tyrosine residue. Subdomain V spans the two lobes.

[0010] The kinases may be categorized into families by the different amino acid sequences (between 5 and 100 residues) located on either side of, or inserted into loops of, the kinase domain. These amino acid sequences allow the regulation of each kinase as it recognizes and interacts with its target protein. The primary structure of the kinase domain is conserved and contains specific residues and identifiable motifs or patterns of amino acids. The serine threonine kinases represent one family which preferentially phosphorylates serine or threonine residues. Many serine threonine kinases, including those from human, rabbit, rat, mouse, and chicken cells and tissues, have been described

(Hardie, G. and Hanks, S. (1995) The Protein Kinase Facts Books, Vol 1:7-20 Academic Press, San Diego, CA).

Matrix Proteins-

[0011] The matrix proteins (MPs) provide structural support, cell and tissue identity, and autocrine, paracrine and juxtacrine properties for most eukaryotic cells (McGowan, S.E. (1992) FASEB J. 6:2895-2904). MPs include adhesion molecules, integrins and selectins, cadherins, lectins, lipocalins, and extracellular matrix proteins (ECMs). MPs possess many different domains which interact with soluble, extracellular molecules. These domains include collagen-like domains, EGF-like domains, immunoglobulin-like domains, fibronectin-like domains, type A domain of von Willebrand factor (vWFA)-like modules, ankyrin repeat modules, RDG or RDG-like sequences, carbohydrate-binding domains, and calcium-binding domains.

[0012] The diversity, distribution and biochemistry of MPs is indicative of their many, overlapping roles in cell proliferation and cell signaling. MPs function in the formation, growth, remodeling, and maintenance of bone, and in the mediation and regulation of inflammation. Biochemical changes that result from congenital, epigenetic, or infectious diseases affect the expression and balance of MPs. This balance, in turn, affects the activation, proliferation, differentiation, and migration of leukocytes and determines whether the immune response is appropriate or self-destructive (Roman, J. (1996) Immunol. Res. 15:163-178).

Fibronectins-

[0013] Fibronectin proteins play a vital role in the structure and function of the extracellular matrix (ECM). Defects in the function of the ECM are thought to be involved in diseases such as osteoporosis, atherosclerosis, arthritis, and fibrotic diseases. Fibronectin enables cells to adhere to the ECM, and influences the growth and migration of cells as well as the organization of the cytoskeleton. As a major component of the ECM, Fibronectin is thought to influence such processes as cellular adhesion and migration, particularly during development, as well as processes such as wound repair (R.O. Hynes, *PNAS*, 96:2588-90 (1999)).

[0014] Fibronectin is a disulfide-linked dimeric glycoprotein composed of type I, type II, and type III fibronectin repeats. Type I repeats are approximately 45 amino acids in length and are located at the amino- and carboxy-termini of the protein. Type II domains are approximately 40-60 amino acids in length, and contain four conserved cysteines involved in disulfide bonding. It is thought that the type II domains may function in collagen binding. There are approximately 15-17 type III domains, arranged in tandem in the middle of the protein, that are thought to provide elasticity to fibronectin.

Defensins-

[0015] Mammalian defensins are produced by the epidermis and mucosal epithelium as innate effector molecules thought to function in an antimicrobial capacity. Defensins are cytotoxic peptides with a broad range of activity on gram-positive and negative bacteria, fungi, parasites, viruses, and mycobacteria. The two characterized defensins are the alpha and beta defensins. The alpha-defensins are produced by neutrophils and macrophage, while the beta-defensins are produced by epithelia (Singh, P.K., et al., *PNAS*, 95:14961-66 (1998); Lillard, J.W., et al., *PNAS*, 96:651-56 (1999)).

[0016] Defensin peptides range in length from approximately 29 to 35 amino acids, and include six conserved cysteine residues involved in disulfide bond formation and protein folding. The distribution and connection of the cysteine residues differs between the alpha and beta defensins.

EF-hand domain containing proteins-

[0017] Calcium is well known to be essential for cell signaling. However, calcium also plays a role in such cellular processes as protein processing and membrane traffic to and through the Golgi. Many proteins thought to be involved in the binding of calcium accomplish this in part through a protein calcium-binding domain known as the EF-hand domain.

[0018] The domain consists of a twelve residue loop flanked by a twelve residue alphahelical domain on both sides. In the EF hand loop, the calcium ion is situated in a coordinated pentagonal bipyramidal configuration. An invariant Glutamic acid or Aspartic acid residue provides two oxygens for liganding the calcium ion.

[0019] Proteins containing this domain include aequorin and Renilla luciferin binding protein (LBP), Recoverins, Calmodulin, Calpain small and large chains, Calretinin, Calcyclin, Fimbrin, Serine/Threonine protein phosphatase, and Diacylglycerol kinase, for example.

MAC/Perforin Family Members-

[0020] The Membrane Attack Complex (MAC) is one of the sequentially activated, membrane bound complexes of the complement system used to eliminate diseased or non-compliant cells. Under this system, activated C5b sequentially binds C6 and C7, which insert into cell membranes. This complex then binds one molecule of C8, followed by between 1 and 18 molecules of C9, which polymerizes to generate a transmembrane channel. These transmembrane channels pierce the membrane, increasing the cell's permeability. These channels permit small molecules in the cell to exchange with the medium. Therefore, water is osmotically drawn into the cell, eventually resulting in the cell bursting.

[0021] Similarly, Perforin is a molecule produced by cytotoxic T cells. In the presence of calcium, Perforin polymerizes into transmembrane channels capable of lysing a variety of target cells in a nonspecific manner.

Pancreatic Hormones-Serine Carboxypeptidases-

[0022] Pancreatic hormone (PP) is a peptide of approximately 80 amino acids in length that is generated in pancreatic islets of Langherhans and consequently secreted. Pancreatic hormone is thought to function as a regulator of pancreatic and gastrointestinal functions.

[0023] Representative members of the pancreatic hormones family of proteins include Neuropeptide Y, Peptide YY, and skin peptide YY. These proteins may be useful as therapeutics for controlling secretion of the gonadotropin-releasing hormone, disorders related to feeding, vasoconstrictory actions, and colonic mobility, as well as antibacterial and antifungal activity.

Serine Carboxypeptidases-

[0024] Carboxypeptidases catalyze the hydrolysis of C-terminal residues of polypeptides. Carboxypeptidases are identified either as metallo-carboxypeptidases or serine-carboxypeptidases.

[0025] Serine carboxypeptidases have the ability to hydrolyze peptides as well as peptide amides from the C-terminus, and have a preferential release of a C-terminal arginine or lysine residue. Their subcellular location is usually extracellular or intracellular. The catalytic activity of serine carboxypeptidases is provided by a charge relay system involving an aspartic acid residue hydrogen-bonded to a histidine, which is itself hydrogen bonded to a serine.

Tumor necrosis factors (TNF)-

Tumor necrosis factors (TNF) alpha and beta are cytokines, which act through TNF receptors to regulate numerous biological processes, including protection against infection and induction of shock and inflammatory disease. The TNF molecules belong to the "TNF-ligand" superfamily, and act together with their receptors or counterligands, the "TNF-receptor" superfamily. So far, nine members of the TNF ligand superfamily have been identified and ten members of the TNF-receptor superfamily have been characterized.

[0027] Many members of the TNF-ligand superfamily are expressed by activated T-cells, implying that they are necessary for T-cell interactions with other cell types which underlie cell ontogeny and functions (Meager, A., supra).

[0028] Considerable insight into the essential functions of several members of the TNF receptor family has been gained from the identification and creation of mutants that abolish the expression of these proteins. For example, naturally occurring mutations in the FAS antigen and its ligand cause lymphoproliferative disease (Watanabe-Fukunaga, R. et al., Nature 356:314 (1992)), perhaps reflecting a failure of programmed cell death. Mutations of the CD40 ligand cause an X-linked immunodeficiency state characterized by high levels of immunoglobulin M and low levels of immunoglobulin G in plasma, indicating faulty T-cell-dependent B-cell activation (Allen, R.C. et al., Science 259:990 (1993)). Targeted mutations of the low affinity nerve growth factor receptor cause a disorder characterized by faulty sensory innovation of peripheral structures (Lee, K.F. et al., Cell 69:737 (1992)).

[0029] TNF and LT- α are capable of binding to two TNF receptors (the 55- and 75-kd TNF receptors). A large number of biological effects elicited by TNF and LT- α , acting through their receptors, include hemorrhagic necrosis of transplanted tumors, cytotoxicity, a role in endotoxic shock, inflammation, immunoregulation, proliferation and anti-viral responses, as well as protection against the deleterious effects of ionizing radiation. TNF and LT- α are involved in the pathogenesis of a wide range of diseases, including endotoxic shock, cerebral malaria, tumors, autoimmune disease, AIDS and graft-host rejection (Beutler, B. and Von Huffel, C., *Science 264*:667-668 (1994)). Mutations in the p55 Receptor cause increased susceptibility to microbial infection.

[0030] Moreover, an about 80 amino acid domain near the C-terminus of TNFR1 (p55) and Fas was reported as the "death domain," which is responsible for transducing signals for programmed cell death (Tartaglia *et al.*, *Cell* 74:845 (1993)).

[0031] Plasma membrane associated proteins with a predominant tissue expression pattern are important targets for targeted drug delivery, tumor-targeted therapy (e.g., including, but not limited to, radioimmunotherapy) antibody mediated attack of diseased tissues or cancers, and immune mediated cytotoxicity.

[0032] The discovery of new plasma membrane associated proteins and the polynucleotides encoding these molecules thus satisfies a need in the art by not only providing new compositions useful in the diagnosis, treatment, and prevention of diseases associated with cell proliferation and cell signaling, particularly cancer, immune response and neuronal disorders; but also by providing new targets for immune based therapies.

Summary of the Invention

[0033] The present invention relates to novel proteins. More specifically, isolated nucleic acid molecules are provided encoding novel polypeptides. Novel polypeptides and antibodies that bind to these polypeptides are provided. Also provided are vectors, host cells, and recombinant and synthetic methods for producing human polynucleotides and/or polypeptides, and antibodies. The invention further relates to diagnostic and therapeutic methods useful for diagnosing, treating, preventing and/or prognosing disorders related to these novel polypeptides. The invention further relates to screening methods for

identifying agonists and antagonists of polynucleotides and polypeptides of the invention. The present invention further relates to methods and/or compositions for inhibiting or enhancing the production and function of the polypeptides of the present invention.

Detailed Description

Tables

[0034] Table 1 summarizes some of the polynucleotides encompassed by the invention (including cDNA clones related to the sequences (Clone ID NO:Z), contig sequences (contig identifier (Contig ID:) and contig nucleotide sequence identifier (SEO ID NO:X)) and further summarizes certain characteristics of these polynucleotides and the polypeptides encoded thereby. The first column provides the gene number in the application for each clone identifier. The second column provides a unique clone identifier, "Clone ID NO:Z", for a cDNA clone related to each contig sequence disclosed in Table 1. The third column provides a unique contig identifier, "Contig ID:" for each of the contig sequences disclosed in Table 1. The fourth column provides the sequence identifier, "SEQ ID NO:X", for each of the contig sequences disclosed in Table 1. The fifth column, "ORF (From-To)", provides the location (i.e., nucleotide position numbers) within the polynucleotide sequence of SEQ ID NO:X that delineate the preferred open reading frame (ORF) that encodes the amino acid sequence shown in the sequence listing and referenced in Table 1 as SEQ ID NO:Y (column 6). Column 7 lists residues comprising predicted epitopes contained in the polypeptides encoded by each of the preferred ORFs (SEQ ID NO:Y). Identification of potential immunogenic regions was performed according to the method of Jameson and Wolf (CABIOS, 4; 181-186 (1988)); specifically, the Genetics Computer Group (GCG) implementation of this algorithm, embodied in the program PEPTIDESTRUCTURE (Wisconsin Package v10.0, Genetics Computer Group (GCG), Madison, Wisc.). This method returns a measure of the probability that a given residue is found on the surface of the protein. Regions where the antigenic index score is greater than 0.9 over at least 6 amino acids are indicated in Table 1 as "Predicted Epitopes". In particular embodiments, polypeptides of the invention comprise, or alternatively consist of, one, two, three, four, five or more of the predicted epitopes described in Table 1. It will be appreciated that depending on the analytical criteria used to predict antigenic determinants, the exact address of the determinant may

vary slightly. Column 8, "Tissue Distribution" shows the expression profile of tissue. cells, and/or cell line libraries which express the polynucleotides of the invention. The first number in column 8 (preceding the colon), represents the tissue/cell source identifier code corresponding to the key provided in Table 4. Expression of these polynucleotides was not observed in the other tissues and/or cell libraries tested. For those identifier codes in which the first two letters are not "AR", the second number in column 8 (following the colon), represents the number of times a sequence corresponding to the reference polynucleotide sequence (e.g., SEQ ID NO:X) was identified in the tissue/cell source. Those tissue/cell source identifier codes in which the first two letters are "AR" designate information generated using DNA array technology. Utilizing this technology, cDNAs were amplified by PCR and then transferred, in duplicate, onto the array. Gene expression was assayed through hybridization of first strand cDNA probes to the DNA array, cDNA probes were generated from total RNA extracted from a variety of different tissues and cell lines. Probe synthesis was performed in the presence of ³³P dCTP, using oligo(dT) to prime reverse transcription. After hybridization, high stringency washing conditions were employed to remove non-specific hybrids from the array. The remaining signal, emanating from each gene target, was measured using a Phosphorimager. Gene expression was reported as Phosphor Stimulating Luminescence (PSL) which reflects the level of phosphor signal generated from the probe hybridized to each of the gene targets represented on the array. A local background signal subtraction was performed before the total signal generated from each array was used to normalize gene expression between the different hybridizations. The value presented after "[array code]:" represents the mean of the duplicate values, following background subtraction and probe normalization. One of skill in the art could routinely use this information to identify normal and/or diseased tissue(s) which show a predominant expression pattern of the corresponding polynucleotide of the invention or to identify polynucleotides which show predominant and/or specific tissue and/or cell expression. Column 9 provides the chromosomal location of polynucleotides corresponding to SEQ ID NO:X. Chromosomal location was determined by finding exact matches to EST and cDNA sequences contained in the NCBI (National Center for Biotechnology Information) UniGene database. Given a presumptive chromosomal location, disease locus association was determined by comparison with the Morbid Map, derived from Online Mendelian Inheritance in Man (Online Mendelian

Inheritance in Man, OMIMTM. McKusick-Nathans Institute for Genetic Medicine, Johns Hopkins University (Baltimore, MD) and National Center for Biotechnology Information, National Library of Medicine (Bethesda, MD) 2000. World Wide Web URL: http://www.ncbi.nlm.nih.gov/omim/). If the putative chromosomal location of the Query overlaps with the chromosomal location of a Morbid Map entry, an OMIM identification number is disclosed in column 10 labeled "OMIM Disease Reference(s)". A key to the OMIM reference identification numbers is provided in Table 5. Column 11 provides the amino acid position of the ALOM hit(s) predicted for the amino acid sequence shown in SEQ ID NO:Y.

Table 2 summarizes homology and features of some of the polypeptides of the [0035] invention. The first column provides a unique clone identifier, "Clone ID NO:Z", corresponding to a cDNA clone disclosed in Table 1. The second column provides the unique contig identifier, "Contig ID:" corresponding to contigs in Table 1 and allowing for correlation with the information in Table 1. The third column provides the sequence identifier, "SEQ ID NO:X", for the contig polynucleotide sequence. The fourth column provides the analysis method by which the homology/identity disclosed in the Table was determined. Comparisons were made between polypeptides encoded by the polynucleotides of the invention and either a non-redundant protein database (herein referred to as "NR"), or a database of protein families (herein referred to as "PFAM") as further described below. The fifth column provides a description of the PFAM/NR hit having a significant match to a polypeptide of the invention. Column six provides the accession number of the PFAM/NR hit disclosed in the fifth column. Column seven, "Score/Percent Identity", provides a quality score or the percent identity, of the hit disclosed in columns five and six. Columns 8 and 9, "NT From" and "NT To" respectively, delineate the polynucleotides in "SEQ ID NO:X" that encode a polypeptide having a significant match to the PFAM/NR database as disclosed in the fifth and sixth In specific embodiments polypeptides of the invention comprise, or columns. alternatively consist of, an amino acid sequence encoded by a polynucleotide in SEQ ID NO:X as delineated in columns 8 and 9, or fragments or variants thereof.

[0036] Table 3 provides polynucleotide sequences that may be disclaimed according to certain embodiments of the invention. The first column provides a unique clone identifier, "Clone ID", for a cDNA clone related to contig sequences disclosed in Table 1. The

second column provides the sequence identifier, "SEQ ID NO:X", for contig sequences disclosed in Table 1. The third column provides the unique contig identifier, "Contig ID:", for contigs disclosed in Table 1. The fourth column provides a unique integer 'a' where 'a' is any integer between 1 and the final nucleotide minus 15 of SEQ ID NO:X, and the fifth column provides a unique integer 'b' where 'b' is any integer between 15 and the final nucleotide of SEQ ID NO:X, where both a and b correspond to the positions of nucleotide residues shown in SEO ID NO:X, and where b is greater than or equal to a + 14. For each of the polynucleotides shown as SEO ID NO:X, the uniquely defined integers can be substituted into the general formula of a-b, and used to describe polynucleotides which may be preferably excluded from the invention. In certain embodiments, preferably excluded from the invention are at least one, two, three, four, five, ten, or more of the polynucleotide sequence(s) having the accession number(s) disclosed in the sixth column of this Table. In further embodiments, preferably excluded from the invention are the specific polynucleotide sequence(s) contained in the clones corresponding to at least one, two, three, four, five, ten, or more of the available material having the accession numbers identified in the sixth column of this Table.

Table 4 provides a key to the tissue/cell source identifier code disclosed in Table 1, column 8. Column 1 provides the tissue/cell source identifier code disclosed in Table 1, Column 8. Columns 2-5 provide a description of the tissue or cell source. Codes corresponding to diseased tissues are indicated in column 6 with the word "disease". The use of the word "disease" in column 6 is non-limiting. The tissue or cell source may be specific (e.g. a neoplasm), or may be disease-associated (e.g., a tissue sample from a normal portion of a diseased organ). Furthermore, tissues and/or cells lacking the "disease" designation may still be derived from sources directly or indirectly involved in a disease state or disorder, and therefore may have a further utility in that disease state or disorder. In numerous cases where the tissue/cell source is a library, column 7 identifies the vector used to generate the library.

[0038] Table 5 provides a key to the OMIM reference identification numbers disclosed in Table 1, column 10. OMIM reference identification numbers (Column 1) were derived from Online Mendelian Inheritance in Man (Online Mendelian Inheritance in Man, OMIM. McKusick-Nathans Institute for Genetic Medicine, Johns Hopkins University (Baltimore, MD) and National Center for Biotechnology Information, National Library of

Medicine, (Bethesda, MD) 2000. World Wide Web URL: http://www.ncbi.nlm.nih.gov/omim/). Column 2 provides diseases associated with the cytologic band disclosed in Table 1, column 9, as determined using the Morbid Map database.

[0039]

Definitions

[0040] The following definitions are provided to facilitate understanding of certain terms used throughout this specification.

[0041] In the present invention, "isolated" refers to material removed from its original environment (e.g., the natural environment if it is naturally occurring), and thus is altered "by the hand of man" from its natural state. For example, an isolated polynucleotide could be part of a vector or a composition of matter, or could be contained within a cell, and still be "isolated" because that vector, composition of matter, or particular cell is not the original environment of the polynucleotide. The term "isolated" does not refer to genomic or cDNA libraries, whole cell total or mRNA preparations, genomic DNA preparations (including those separated by electrophoresis and transferred onto blots), sheared whole cell genomic DNA preparations or other compositions where the art demonstrates no distinguishing features of the polynucleotide/sequences of the present invention.

[0042] As used herein, a "polynucleotide" refers to a molecule having a nucleic acid sequence encoding SEQ ID NO:Y or a fragment or variant thereof; a nucleic acid sequence contained in SEQ ID NO:X (as described in column 3 of Table 1) or the complement thereof; a cDNA sequence contained in Clone ID NO:Z (as described in column 2 of Table 1 and contained within the ATCC Deposit). For example, the polynucleotide can contain the nucleotide sequence of the full length cDNA sequence, including the 5' and 3' untranslated sequences, the coding region, as well as fragments, epitopes, domains, and variants of the nucleic acid sequence. Moreover, as used herein, a "polypeptide" refers to a molecule having an amino acid sequence encoded by a

polynucleotide of the invention as broadly defined (obviously excluding poly-Phenylalanine or poly-Lysine peptide sequences which result from translation of a polyA tail of a sequence corresponding to a cDNA).

[0043] In the present invention, "SEQ ID NO:X" was often generated by overlapping sequences contained in multiple clones (contig analysis). A representative clone containing all or most of the sequence for SEQ ID NO:X is deposited at Human Genome Sciences, Inc. (HGS) in a catalogued and archived library. As shown, for example, in column 2 of Table 1, each clone is identified by a cDNA Clone ID (identifier generally referred to herein as Clone ID NO:Z). Each Clone ID is unique to an individual clone and the Clone ID is all the information needed to retrieve a given clone from the HGS library. Furthermore, clones disclosed in this application have been deposited with the ATCC on March 24, 2000, having the ATCC designation numbers PTA-1559. The ATCC is located at 10801 University Boulevard, Manassas, Virginia 20110-2209, USA. The ATCC deposits were made pursuant to the terms of the Budapest Treaty on the international recognition of the deposit of microorganisms for the purposes of patent procedure.

[0044] In specific embodiments, the polynucleotides of the invention are at least 15, at least 30, at least 50, at least 100, at least 125, at least 500, or at least 1000 continuous nucleotides but are less than or equal to 300 kb, 200 kb, 100 kb, 50 kb, 15 kb, 10 kb, 7.5kb, 5 kb, 2.5 kb, 2.0 kb, or 1 kb, in length. In a further embodiment, polynucleotides of the invention comprise a portion of the coding sequences, as disclosed herein, but do not comprise all or a portion of any intron. In another embodiment, the polynucleotides comprising coding sequences do not contain coding sequences of a genomic flanking gene (i.e., 5' or 3' to the gene of interest in the genome). In other embodiments, the polynucleotides of the invention do not contain the coding sequence of more than 1000, 500, 250, 100, 50, 25, 20, 15, 10, 5, 4, 3, 2, or 1 genomic flanking gene(s).

[0045] A "polynucleotide" of the present invention also includes those polynucleotides capable of hybridizing, under stringent hybridization conditions, to sequences contained in SEQ ID NO:X, or the complement thereof (e.g., the complement of any one, two, three, four, or more of the polynucleotide fragments described herein), the polynucleotide sequence delineated in columns 8 and 9 of Table 2 or the complement thereof, and/or cDNA sequences contained in Clone ID NO:Z (e.g., the complement of any one, two, three, four, or more of the polynucleotide fragments, or the cDNA clone within the pool of

cDNA clones deposited with the ATCC, described herein). "Stringent hybridization conditions" refers to an overnight incubation at 42 degree C in a solution comprising 50% formamide, 5x SSC (750 mM NaCl, 75 mM trisodium citrate), 50 mM sodium phosphate (pH 7.6), 5x Denhardt's solution, 10% dextran sulfate, and 20 µg/ml denatured, sheared salmon sperm DNA, followed by washing the filters in 0.1x SSC at about 65 degree C.

[0046] Also contemplated are nucleic acid molecules that hybridize to the polynucleotides of the present invention at lower stringency hybridization conditions. Changes in the stringency of hybridization and signal detection are primarily accomplished through the manipulation of formamide concentration (lower percentages of formamide result in lowered stringency); salt conditions, or temperature. For example, lower stringency conditions include an overnight incubation at 37 degree C in a solution comprising 6X SSPE (20X SSPE = 3M NaCl; 0.2M NaH₂PO₄; 0.02M EDTA, pH 7.4), 0.5% SDS, 30% formamide, 100 ug/ml salmon sperm blocking DNA; followed by washes at 50 degree C with 1XSSPE, 0.1% SDS. In addition, to achieve even lower stringency, washes performed following stringent hybridization can be done at higher salt concentrations (e.g. 5X SSC).

[0047] Note that variations in the above conditions may be accomplished through the inclusion and/or substitution of alternate blocking reagents used to suppress background in hybridization experiments. Typical blocking reagents include Denhardt's reagent, BLOTTO, heparin, denatured salmon sperm DNA, and commercially available proprietary formulations. The inclusion of specific blocking reagents may require modification of the hybridization conditions described above, due to problems with compatibility.

[0048] Of course, a polynucleotide which hybridizes only to polyA+ sequences (such as any 3' terminal polyA+ tract of a cDNA shown in the sequence listing), or to a complementary stretch of T (or U) residues, would not be included in the definition of "polynucleotide," since such a polynucleotide would hybridize to any nucleic acid molecule containing a poly (A) stretch or the complement thereof (e.g., practically any double-stranded cDNA clone generated using oligo dT as a primer).

[0049] The polynucleotide of the present invention can be composed of any polyribonucleotide or polydeoxribonucleotide, which may be unmodified RNA or DNA or modified RNA or DNA. For example, polynucleotides can be composed of single- and

double-stranded DNA, DNA that is a mixture of single- and double-stranded regions, single- and double-stranded RNA, and RNA that is mixture of single- and double-stranded regions, hybrid molecules comprising DNA and RNA that may be single-stranded or, more typically, double-stranded or a mixture of single- and double-stranded regions. In addition, the polynucleotide can be composed of triple-stranded regions comprising RNA or DNA or both RNA and DNA. A polynucleotide may also contain one or more modified bases or DNA or RNA backbones modified for stability or for other reasons. "Modified" bases include, for example, tritylated bases and unusual bases such as inosine. A variety of modifications can be made to DNA and RNA; thus, "polynucleotide" embraces chemically, enzymatically, or metabolically modified forms.

The polypeptide of the present invention can be composed of amino acids [0050] joined to each other by peptide bonds or modified peptide bonds, i.e., peptide isosteres, and may contain amino acids other than the 20 gene-encoded amino acids. The polypeptides may be modified by either natural processes, such as posttranslational processing, or by chemical modification techniques which are well known in the art. Such modifications are well described in basic texts and in more detailed monographs, as well as in a voluminous research literature. Modifications can occur anywhere in a polypeptide, including the peptide backbone, the amino acid side-chains and the amino or carboxyl termini. It will be appreciated that the same type of modification may be present in the same or varying degrees at several sites in a given polypeptide. Also, a given polypeptide may contain many types of modifications. Polypeptides may be branched, for example, as a result of ubiquitination, and they may be cyclic, with or without branching. Cyclic, branched, and branched cyclic polypeptides may result from posttranslation natural processes or may be made by synthetic methods. Modifications include acetylation, acylation, ADP-ribosylation, amidation, covalent attachment of flavin, covalent attachment of a heme moiety, covalent attachment of a nucleotide or nucleotide derivative, covalent attachment of a lipid or lipid derivative, covalent attachment of phosphotidylinositol, cross-linking, cyclization, disulfide bond formation, demethylation, formation of covalent cross-links, formation of cysteine, formation of pyroglutamate, formylation, gamma-carboxylation, glycosylation, GPI anchor formation, hydroxylation, iodination, methylation, myristoylation, oxidation, pegylation, proteolytic processing, phosphorylation, prenylation, racemization, selenoylation, sulfation, transfer-RNA

mediated addition of amino acids to proteins such as arginylation, and ubiquitination. (See, for instance, PROTEINS - STRUCTURE AND MOLECULAR PROPERTIES, 2nd Ed., T. E. Creighton, W. H. Freeman and Company, New York (1993); POSTTRANSLATIONAL COVALENT MODIFICATION OF PROTEINS, B. C. Johnson, Ed., Academic Press, New York, pgs. 1-12 (1983); Seifter et al., Meth. Enzymol. 182:626-646 (1990); Rattan et al., Ann. N.Y. Acad. Sci. 663:48-62 (1992)).

"SEQ ID NO:X" refers to a polynucleotide sequence described, for example, in Tables 1 or 2, while "SEQ ID NO:Y" refers to a polypeptide sequence described in column 6 of Table 1. SEQ ID NO:X is identified by an integer specified in column 4 of Table 1. The polypeptide sequence SEQ ID NO:Y is a translated open reading frame (ORF) encoded by polynucleotide SEQ ID NO:X. "Clone ID NO:Z" refers to a cDNA clone described in column 2 of Table 1.

[0052] "A polypeptide having functional activity" refers to a polypeptide capable of displaying one or more known functional activities associated with a full-length (complete) protein. Such functional activities include, but are not limited to, biological activity, antigenicity [ability to bind (or compete with a polypeptide for binding) to an anti-polypeptide antibody], immunogenicity (ability to generate antibody which binds to a specific polypeptide of the invention), ability to form multimers with polypeptides of the invention, and ability to bind to a receptor or ligand for a polypeptide.

[0053] The polypeptides of the invention can be assayed for functional activity (e.g. biological activity) using or routinely modifying assays known in the art, as well as assays described herein. Specifically, one of skill in the art may routinely assay polypeptides (including fragments and variants) of the invention for activity using assays as described in the Examples.

[0054] "A polypeptide having biological activity" refers to a polypeptide exhibiting activity similar to, but not necessarily identical to, an activity of a polypeptide of the present invention, including mature forms, as measured in a particular biological assay, with or without dose dependency. In the case where dose dependency does exist, it need not be identical to that of the polypeptide, but rather substantially similar to the dose-dependence in a given activity as compared to the polypeptide of the present invention (i.e., the candidate polypeptide will exhibit greater activity or not more than about 25-fold less and, preferably, not more than about tenfold less activity, and most preferably, not

more than about three-fold less activity relative to the polypeptide of the present invention).

[0055] Table 1 summarizes some of the polynucleotides encompassed by the invention (including contig sequences (SEQ ID NO:X) and clones (Clone ID NO:Z) and further summarizes certain characteristics of these polynucleotides and the polypeptides encoded thereby.

Polynucleotides and Polypeptides of the Invention

It has been discovered herein that the polynucleotides described in Table 1 are predicted to be localized to the plasma membrane of human cells. Accordingly, such polynucleotides, polypeptides encoded by such polynucleotides, and antibodies specific for such polypeptides find use in the diagnosis, treatment, and prevention of diseases associated with cell proliferation and cell signaling, particularly cancer, immune response and neuronal disorders.

Plasma membrane localization was predicted using the following method. All novel contigs in the HGS database were scored using the ALOM program developed by Klein et al. to detect potential transmembrane segments (Klein, P. et al. Biochim. Biophys. Acta 815:468 (1985); which is hereby incorporated by reference in its entirety herein). ALOM attempts to identify the most probable transmembrane segment from the average hydrophobicity value of 17-residue segments, if any. It predicts whether the segment is a transmembrane segment (INTEGRAL) or not (PERIPHERAL) comparing the discriminant score (reported as 'value') with a threshold parameter pre- defined to 0.0 for bacteria ('threshold'). For an integral membrane protein, position(s) of transmembrane segment(s) are also reported. Their length is fixed to 17 but their extension, i.e., the maximal range that satisfies the discriminant criterion, is also given in parentheses. The discrimination step mentioned above is continued after leaving out the segment till there remains no predicted transmembrane segment. The item 'count' is the number of predicted transmembrane segments.

The protein sequence used was the longest start-codon to stop-codon (or end of sequence) ORF. If the ORF was at least 100 amino acids long, and there was a predicted INTEGRAL membrane domain starting at least 40 amino acids downstream of the start

Met, the contig was selected as encoding a plasma-membrane-associated protein. The polynucleotides of the invention are predicted to be plasma membrane associated and comprise the predicted INTEGRAL membrane domains for each unique contig ID shown in column 11 of Table 1.

TABLE 1

ALOM	Results			44-60							104-120,	83-99						80-104,	20-37, 56-	72, 134-	150			40-57		
OMIM	Disease	Reference(s):																								
Cytologic	Band																									
Tissue Distribution	Library code: count	(see Table IV for Library		AR039: 9, AR033: 5,		AR096: 4, AR104: 4,	AR055: 4, AR060: 4,	AR052: 3, AR061: 3	L0619: 1, H0059: 1 and	H0423: 1.	AR055: 15, AR060: 9,	AR052: 7, AR061: 7,	AR089: 6, AR033: 6,	AR053: 5, AR096: 3,	AR104: 1, AR039: 0	L0748: 2, H0328: 1 and	H0529: 1.	AR060: 6, AR055: 3,	AR053: 3, AR096: 2,	AR089: 2, AR061: 2,	AR033: 2, AR052: 1,	AR039: 1, AR104: 1	H0031: 1	AR055: 9, AR060. 6,	AR096: 5, AR089: 5,	AR033: 4, AR052: 4,
Predicted Epitopes				1416 Arg-23 to Leu-33,	Thr-61 to Phe-73.																					
AA	SEQ		NO: Y	1416							[417							1418						1419		
ORF	(From-	To)	_	64 - 471							- #1	572						81 - 530						171 -	530	
SEQ	<u> </u>	NO: X	,	=							12							13						14		
Contig	ID:			413036							456287						•	463734						465120		
Clone ID	NO: Z			HCFNH88							HODDW3	7						HPMFI38						HLTDP38		
Gene	Ž0:			_							1 2							3				- <u>-</u>		4		

	90-113, 59-78, 2- 18, 28-44	31-57, 63- 85, 4-23	126-143
			126650, 126650, 164860, 180105, 222800,
	4		7q31
AR061: 4, AR053: 3, AR039: 2, AR104: 1 L0662: 3, L0803: 2, L0805: 2, T0002: 1, H0090: 1, H0412: 1, L0794: 1, L0804: 1, L0655: 1, L0647: 1, L0666: 1 and L0663: 1.	AR055: 6, AR060: 4, AR052: 4, AR061: 3, AR039: 3, AR089: 3, AR053: 3, AR096: 3, AR033: 3, AR104: 2 L0615: 1, S0420: 1, H0333: 1, H0286: 1, H0634: 1, H0144: 1 and HC423: 1.	AR053: 8, AR055: 5, AR053: 3, AR089: 3, AR052: 3, AR061: 3, AR039: 3, AR060: 3, AR104: 2, AR096: 2 L0756: 4, L0439: 2, S0412: 2, S0222: 1, H0327: 1, H0009: 1, L0157: 1 and S0031: 1.	AR089: 7, AR096: 6, AR053: 5, AR060: 5, AR052: 4, AR039: 4, AR104: 4, AR055: 4, AR033: 3, AR061: 1
	Gln-20 to Ala-26, Ser-53 to Glu-60.		Met-1 to Phe-6, Ser-12 to Asp-17, Ser-100 to Ser-105, Arg-163 to Asp-176, Val-192 to Glu-199.
	1420	1421	1422
	15 - 365	595	67 - 723
	15	16	17
		466000	488966
	нмнвт30	HFCBA57	HSRAL33
	N	9	7

	89-105	72-90
246900, 274600, 274600, 602081		
1:00:40	AR055: 8, AR052: 5, AR033: 4, AR061: 4, AR060: 4, AR089: 3, AR096: 3, AR039: 3, AR104: 3, AR053: 3 L0596: 2, L0588: 2, H0135: 1, H0056: 1, L0369: 1, L0803: 1, H0520: 1, S0027: 1 and S0276: 1.	Leu-9 to Arg-18, AR060: 140, AR055: 117, Phe-109 to Gly-115. AR104: 113, AR039: 111, AR061: 92, AR033: 72, AR053: 70, AR052: 66, AR089: 55, AR096: 21 L0748: 5, L0779: 2, L0731: 2, H0556: 1, S0356: 1, H0575: 1, H0597: 1, H0551:
	Pro-52 to Pro-57.	
	1423	1424
	20 - 415	74 - 424
	18	19
L	502907	503441
	HSSMQ84	HUKAB82
	∞	6

	52-68	100-118
9: 1, 1, L0655: 3: 1, 6: 1.	3: 3, 3: 2, 3: 1, 4: 1 2, 2, H0295: 4: 1, 1, H0545: 1: 1, 1: 1,	3: 5, 5: 4, 3: 3, 9: 2, 1: 2 2, 1: 2, 1: 2, 2, 1: 2, 3: 2, 3: 2,
1, H0413: 1, H0059: 1, L0770: 1, L0771: 1, L0655: 1, H0144: 1, S0378: 1, L0747: 1 and S0276: 1.	AR096: 4, AR033: 3, AR039: 3, AR089: 3, AR055: 3, AR052: 2, AR061: 2, AR053: 1, AR060: 1, AR104: 1 L0766: 4, H0617: 2, L0662: 2, H0690: 2, H0295: 1, H0662: 1, S0354: 1, H0729: 1, H0318: 1, H0545: 1, H0266: 1, H0401: 1, H0135: 1, H087: 1, L5575: 1, L0803: 1, L0523: 1, L0383: 1, L0665: 1, H0703: 1, H0539: 1, H0521: 1, H0522: 1, S0406: 1, S0028: 1, L0779: 1 and H0352: 1.	AR052: 5, AR053: 5, AR096: 4, AR055: 4, AR089: 4, AR033: 3, AR060: 3, AR039: 2, AR104: 2, AR061: 2 L0775: 3, H0624: 2, L0471: 2, S0051: 2, L0768: 2, H0659: 2, L0759: 2, L0605: 2, S0192: 2, S0114:
1, H L07 1, H L07	ARC ARC ARC LOG LOG 1, H HO1 1, L HO5 1, L HO5 1, L	. 6
		1426 Met-1 to Arg-11, Gly-30 to Arg-39.
	1425	1426
	29 - 328	72 - 425
	20	21
	506828	506893
	HDPPP46	HMTME11
	10	

	9-41, 83-
0-66-86-11	AR055: 11, AR060: 8, AR033: 5, AR061: 5, AR052: 5, AR089: 4, AR104: 4, AR096: 4, AR039: 4, AR053: 4 L0439: 4, L0803: 3, H0590: 2, L0483: 2, H0163: 2, L0805: 2, S0374: 2, H0658: 2, H0696: 2, H0717: 1, S0116: 1, S0358: 1, L0717: 1, H0052: 1, H0194: 1, H0184: 1, L0738: 1, H0545: 1, S0316: 1, S0003: 1, S0364: 1, S0366: 1, S0036: 1, H0272: 1, L0638:
	12 HBMUK46 507310 22 12 - 386 1427

	8-24 8-24	62-89, 25- 46
1, L0766: 1, L0776: 1, L0789: 1, L0664: 1, L0665: 1, H0710: 1, H0521: 1, S0013: 1, S0406: 1, L0744: 1, L0752: 1, L0758: 1, L0605: 1, S0026: 1 and H0543: 1.	AR052: 319, AR096: 250, AR089: 171, AR060: 143, AR053: 121, AR104: 71, AR039: 57, AR033: 51, AR061: 51, AR055: 14 L0752: 3, L0748: 2, L0740: 2, L0731: 2, S0358: 1, H0438: 1, H0574: 1, H0046: 1, H0041: 1, H0272: 1, S0150: 1, L0794: 1, L0803: 1, L0804: 1, L0775: 1, L0661: 1, L0789: 1, H0672: 1, H0539: 1, L0758: 1 and S0436: 1.	AR033: 1, AR089: 1, AR053: 1, AR104: 1, AR061: 1, AR096: 0, AR055: 0, AR060: 0, AR052: 0 L0766: 6, L0740: 5, H0135: 1, L0769: 1, L0383: 1, S0044: 1, L0750: 1 and
		Pro-15 to Ser-21, Ser-60 to Tyr-65, Glu-90 to Asp-101.
	1428	1429
	25 - 597	60 - 362
	23	24
	509728	521848
	HETDT70	HPWBL19
	13	41

	88-104, 49-65	96-113
L0752: 1.	AR033: 2, AR053: 2, AR089: 1, AR104: 1, AR061: 1, AR055: 1, AR060: 1, AR096: 0, AR039: 0, AR052: 0 S0007: 2, H0392: 2, L0745: 1, L0753: 1, L0759: 1 and L0589: 1.	AR104: 1, AR096: 1, AR033: 1, AR089: 1, AR060: 1, AR061: 1, AR052: 0, AR055: 0, AR053: 0, AR039: 0 L0766: 5, L0438: 4, L0439: 4, L0803: 3, L0759: 3, H0445: 3, H0046: 2, L0157: 2, L0774: 2, L0776: 2, L0774: 2, L0776: 2, L0774: 2, L0776: 2, L0778: 2, L0779: 2, L0778: 2, L0779: 2, L0778: 2, L0776: 1, H0459: 1, S0418: 1, L0005: 1, H0580: 1, S0046: 1, H0612: 1, H0586: 1, H0612: 1, H0586: 1, H0659: 1, S0426: 1, H0659: 1, L0638: 1, L0667: 1,
		Lys-12 to Lys-17, Thr-39 to Lys-45, Thr-49 to Glu-57, Thr-59 to Glu-69, Glu-80 to Ile-90, Gly-122 to Met-127, Lys-170 to Asn-177. I
		1431
	1 '	68 - 598
	25	56
	L	524559
	IIMKAD85	HE9NE12
	15	91

201.12	81-102, 22-38	64-80, 15- 31
18370	1463 / 0	
	czdo	ii ii
L0373: 1, L0378: 1, L0805: 1, L0659: 1, L0526: 1, L0809: 1, L0663: 1, S0374: 1, H0711: 1, H0670: 1, H0521: 1, L0777: 1, L0780: 1, L0485: 1, L0097: 1, S0192: 1, H0543: 1, H0423: 1 and H0506: 1.	AR052: 3, AR061: 4, AR052: 3, AR055: 3, AR039: 3, AR060: 3, AR089: 2, AR096: 2, AR033: 1, AR104: 1 H0170: 2	AR055: 16, AR061: 7, AR052: 7, AR060: 6, AR033: 5, AR089: 5, AR039: 0, AR104: 0 H0052: 5, L0748: 5, L0756: 4, L0731: 4, S0360: 3, L0764: 3, L0747: 3, L0749: 3, H0255: 2, H0333: 2, L0055: 2, L0653: 2, L0740: 2, L0754: 2, L0750: 2, L0596: 2, H0352: 2, H0556: 1, H0341: 1, H0662: 1, H0306: 1, H0402: 1, H0036: 1, H0434: 1, H0150:
1 1 1 1 1 1 1 1 1 1		Arg-56 to Phc-61. A A A A A A A A A A A A A A A A A A A
2 - 317	7	376 1433
- 61 - 70		28 53 -
3 525950		99 527491
THEORY 73		18 HHGBV89

	48-65	125-157, 4-29, 67- 86, 36-52, 106-122
1, H0252: 1, L0456: 1, H0135: 1, H0413: 1, H0059: 1, H0529: 1, L0770: 1, L0769: 1, L0630: 1, L0521: 1, L0662: 1, L0775: 1, L0776: 1, L0493: 1, H0684: 1, S0328: 1, S0044: 1, L0777: 1, L0752: 1, L0755: 1, L0758: 1 and S0242: 1.	AR039: 14, AR055: 14, AR033: 11, AR053: 11, AR052: 11, AR060: 10, AR104: 10, AR096: 9, AR089: 8, AR061: 8 S0380: 2, L0742: 2, L0779: 2, L0759: 2, H0333: 1, H0039: 1, H0040: 1, H0625: 1, H0561: 1, L0666: 1, L0663: 1, H0672: 1, L0747: 1, L0777: 1, L0758: 1 and H0444: 1.	AR089: 1, AR061: 1, AR053: 1, AR096: 1, AR060: 1, AR104: 1, AR033: 0, AR055: 0, AR039: 0, AR052: 0 L0777: 5, S0436: 5, S0116: 3, L0805: 3, L0809: 3, H0696: 3, H0423: 3, S0282:
	Lys-13 to Asp-24, Pro-32 to Arg-40.	Asn-54 to Gly-60, Pro-166 to Pro-171.
	1434	1435
	1 - 405	531 - 16
	59	30
	529791	532045
	HTTDC06	HFXKR35
	61	50

		56-73
2, \$0354: 2, H0083: 2, H0316: 2, L0763: 2, L0767: 2, L0776: 2, \$0406: 2, L0779: 2, \$0114: 1, H0657: 1, H0656: 1, \$0358: 1, \$0444: 1, \$0360: 1, H0340: 1, \$0046: 1, H0619: 1, H0455: 1, H0333: 1, H0574: H06560: 1, H0333: 1, H0574: H06560: 1, H0633: 1, H0574: H06560: 1, H0633: 1, H0574: H06560: 1, H06340: 1, H06560: 1, H0660:	1, 1102.55; 1, 101.05; 1, H0156; 1, L0021; 1, T0074; 1, H0618; 1, H0318; 1, S0474; 1, S0049; 1, H0327; 1, H0530; 1, H0615; 1, H0653; 1, H0673; 1, H065; 1, L0520; 1, L0769; 1, L0761; 1, L0521; 1, L0774; 1, L0665; 1, L0665; 1, L0666; 1, L0664; 1, H0659; 1, H0618; 1, S0268; 1, S0176; 1, H0478; 1, S0268; 1, L0731; 1, L0608; 1, L0362; 1, S0026; 1 and S0242; 1,	AR055: 4, AR039: 3, AR060: 2, AR033: 2, AR053: 2, AR061: 2,
		Ser-7 to Gln-20, Pro-24 to Phe-34, Gly-76 to Gly-84.
		3 1436
		17 - 373
		534414 31
		HHSDL85
		21

	49-65	49-65	46-62, 26-
		·	114240, 224120, 600839, 602099
			15q15.1
AR104: 2, AR089: 2, AR096: 2, AR052: 2 S0007: 3, S0001: 1, H0618: 1, H0009: 1, S0051: 1, L0763: 1, L0439: 1 and L0758: 1.	AR033: 54, AR055: 51, AR061: 43, AR089: 40, AR053: 38, AR060: 38, AR052: 26, AR096: 11, AR104: 10, AR039: 5 H0038: 2	AR033: 112, AR052: 80, AR096: 68, AR053: 67, AR089: 65, AR104: 61, AR060: 58, AR061: 55, AR039: 52, AR055: 38 H0052: 2, H0616: 2, L0779: 2, L0777: 2, H0656: 1, H0549: 1, H0038: 1, L0748: 1, L0758: 1, L0601: 1 and H0543: 1.	AR055: 17, AR053: 9, AR060: 9, AR033: 9, AR061: 8, AR039: 7, AR089: 6, AR052: 6, AR104: 6, AR096: 5 S0418: 3, L0439: 3, L0595: 2, H0542: 2, H0656:
	Pro-15 to Thr-24, Glu-39 to Trp-47.	Arg-14 to Asp-20.	
	1437	1438	1439
	88 - 438	37 - 453	156 - 488
	32	33	ਲ ਲ
	535036	535040	536712
	HTECA32	HTEHL79	HPJBL54
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	Thr-116 to Gly-122, A Lys-142 to Pro-150, Pro-164 to Ala-172, A Glu-184 to Asn-189.	Glu-9 to Gly-14, Gln-75 to Val-81, Ser-94 to Gly-116.
	1988	1989
	31 - 873	775 -
	583	584
	859200	859201
	HTXPN78	HFPGR87
	573	574

	252-280, 319-342, 202-222, 157-173, 385-401, 174-190
9474: 0231: 0615: 1497: 7749:	748: 7223: 586: 616:
1, S0222: 1, H0441: 1, H0392: 1, H0333: 1, S0474: 1, H0052: 1, H0194: 1, H0235: 1, H0194: 1, H0620: 1, H0150: 1, H0620: 1, H0150: 1, H0674: 1, H0163: 1, L0497: 1, L0804: 1, L0661: 1, L0543: 1, L0791: 1, L5286: 1, H0144: 1, S0126: 1, H0696: 1, L0743: 1, L0749: 1, L0780: 1, L0752: 1, L0758: 1, S0031: 1, L0591:	AR052: 8, AR055: 8, AR053: 6, AR096: 6, AR089: 5, AR060: 4, AR033: 4, AR039: 4, AR061: 3, AR104: 3 L0758: 4, S0358: 3, L0758: 4, S0358: 3, L0754: 2, L0756: 2, L0759: 2, H0265: 1, H0223: 1, H0222: 1, H0159: 1, L0002: 1, S0116: 1, H0586: 1, T0040: 1, H0013: 1, H0050: 1, T0110: 1, L0157: 1, H0050: 1, H0266: 1, S0250: 1, S0364: 1, H0616:
	990 Pro-12 to Lys-33, Asn-41 to His-46, Pro-48 to Ser-58, Gly-71 to Asp-78, Ala-94 to Gly-102, Ser-133 to Ser-140, Arg-197 to Lys-202.
	1990
	98 1402
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	727-762, 5-21, 556- 572	
1, H0264: 1, H0509: 1, H0641: 1, L0646: 1, L0773: 1, L0662: 1, L0776: 1, L0655: 1, L0664: 1, S0126: 1, S0380: 1, H0521: 1, L0779: 1, L0593: 1, S0242: 1 and L0697: 1.	Fig. HDTDZ65 859250 586 35 - 1991 Leu-55 to Phe-61, AR089: 5, AR052: 2, Arg-105 to Cys-111, AR060: 2, AR096: 2, Leu-152 to Glu-158, AR055: 2, AR033: 1, Glu-174 to Leu-187, AR039: 1, AR061: 1, Tyr-213 to Pro-223, AR104: 0, AR053: 0, Ala-246 to Asp-256, S0192: 18, H0521: 7, Leu-274 to Cys-283, L0659: 6, S0126: 6, L0744: Glu-297 to Tyr-302, 6, H0486: 5, L0666: 5, Pro-322 to Leu-327, S0022: 4, L0438: 4, L0754: Asp-333 to Val-343, 4, S0194: 4, S0045: 3, Thr-375 to Pro-382, L0662: 3, S0330: 3, L0758: Asp-403 to Ser-415, 3, S0040: 2, H0661: 2, Thr-490 to Lys-496, H0662: 2, S0132: 2, S0476: Pro-531 to Asp-541, 2, H0392: 2, H0013: 2, Arg-545 to Gly-551, H0622: 2, H0581: 2, S0230: 3, H0622: 2, H0581: 2, H0622: 2, H0581: 2, H0622: 2, H0581: 2, H0622: 2, H0581: 2, H0622: 2, H0651: 2, H0622: 2, H0622: 2, H0651: 2, H0622: 2, H0622: 2, H0651: 2, H0622: 2, H0622: 2, H0621: 2, H0622: 2, H0622: 2, H0622: 2, H0621: 2, H0622: 2, H06	2, F0525. 2, F0474. 2, 80002: 2, S0426: 2, L0771: 2, L0803: 2, L0527: 2, L0664: 2, L0665: 2, H0144: 2, S0027: 2, S0028: 2,

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S0206: 2, L0740: 2, L0751: 2, H0595: 2, L0596: 2,	Н0506: 2, Н0170: 1, Т0049.	1, S0212: 1, H0638: 1,	20. 1, 30442. 1, 303 / 0. 0468: 1, S0046: 1.	S0278: 1, H0369: 1, H0592:	0586: 1, S0010: 1,	H0705: 1, H0310: 1, H0046:	0010: 1, H0375: 1,	H0266: 1, H0687: 1, S0214:	0039: 1, L0483: 1,	H0030: 1, H0031: 1, H0032:)366: 1, H0598: 1,	H0038: 1, H0380: 1, H0268:	., H0413: 1, H0056: 1,	S0440: 1, H0652: 1, S0142:	344: 1, L0770: 1,	.0638: 1, L0646: 1, L0649:	3381: 1, L0806: 1,	.0657: 1, L0658: 1, L0518:	., L0809: 1, L0789: 1,	H0682: 1, S0332: 1, H0696:	1, S0404: 1, S0406: 1,	55: 1, H0627: 1, S0037:	1, S3014: 1, L0747: 1,	55: 1, L0757: 1, L0588:	3591: 1, S0026: 1,	H0653: 1, H0665: 1 and	96: 1.
S020 2, H	H050	1, SC	1. SC	8027	1, H(H070	1, TC	H026	1, H((100)	1, 50	(100H)	1, H(8044	1, S0	[7063	1, LC	5907	1, LC	390H	1, SC	H055	11, S3	L075	1, LC	590H	80196:
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46-74, 77- 98	
AR033: 5, AR096: 3, AR060: 3, AR052: 3, AR089: 3, AR053: 2, AR104: 1, AR061: 1, AR055: 1, AR039: 0 L0439: 6, L0659: 4, L0740: 4, L0752: 4, S0376: 3, L0731: 3, H0052: 2, L0471: 2, S0051: 2, H0428: 2, H0090: 2, L0803: 2, L0809: 2, H0423: 2, S0452: 2, H0624: 1, H0170: 1, H0663: 1, S0442: 1, S0045: 1, S0220: 1, H0331: 1, S0280: 1, L0021: 1, H0575: 1, H0004: 1, H0083: 1, H0457: 1, H0014: 1, S0388: 1, H0688: 1, H0031: 1, H0553: 1, H0628: 1, L0564: 1, S0210: 1, S0422: 1, L0598: 1, L0768: 1, L0794: 1, L0768: 1, L0774: 1	L0775: 1, L0518: 1, L0666: 1, L0664: 1, H0547: 1, H0659: 1, H0539: 1, S0380: 1, H0478: 1, H0479: 1,
992 Met-7 to Asp-22.	
1992	
93 - 440	
287	
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							- 3				Ala-216 to Tyr-223.																	
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				13 - 318						- 861	875																	
				588						685																		
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				HOHAV17						HNTAW95																		
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	33-70, 78- 99, 7-24, 57-73, 117-133	153-169
1, L0592: 1, L0593: 1, L0595: 1 and H0506: 1.	AR052: 8, AR096: 7, AR060: 7, AR060: 7, AR089: 6, AR033: 6, AR061: 5, AR039: 5, AR104: 3 H0521: 7, L0748: 4, H0556: 3, H0586: 2, H0264: 2, L0740: 2, S0436: 2, H0252: 1, S0040: 1, H0294: 1, S0134: 1, H0583: 1, H0428: 1, S0356: 1, S0045: 1, H0069: 1, H0284: 1, H0428: 1, S0036: 1, H0428: 1, S036: 1, H0551: 1, H0494: 1, S0144: 1, L0807: 1, L0790: 1, H0549: 1, S0152: 1, S0028: 1, S0032: 1, L0750: 1, L0777: 1, L0777: 1, L0759: 1, H0445: 1 and H0422: 1	Met-1 to Lys-17, AR096: 5, AR089: 4, Asn-66 to Asn-95, AR033: 4, AR060: 3, Thr-100 to Tyr-106. AR052: 1, AR061: 1, AR104: 0, AR053: 0
	1995	1996
	824 824	103 -
	290	591
	859704	859756
	HMCFL79	HNTCT36
	280	581

	74-97, 3-	55-81, 36-
		188826, 250100, 250800, 250800
		22q13.2- q13.31
H0519: 2, H0156: 1, L0666: 1, L0665: 1, H0520: 1, L0758: 1 and L0759: 1.	AR033: 10, AR055: 10, AR052: 8, AR089: 7, AR060: 7, AR053: 7, AR061: 6, AR096: 5, AR104: 3, AR039: 1 L0766: 3, L0731: 3, S0051: 2, L0769: 2, L0662: 2, L0768: 2, L0747: 2, H0140: 1, H0656: 1, S0418: 1, S0444: 1, H0013: 1, L0021: 1, H0046: 1, H0439: 1, L0763: 1, L0372: 1, L0794: 1, L0805: 1, L0783: 1, L0809: 1, L0647: 1, L0788: 1, L0792: 1, L0663: 1, L0664: 1, H0691: 1, H0593: 1, L0750: 1 and L0758: 1.	AR039: 1, AR096: 1, AR033: 1, AR061: 1, AR060: 0, AR089: 0, AR052: 0, AR055: 0, AR104: 0 L0769: 5, S0045: 2,
	Pro-30 to Arg-35, Glu-41 to Glu-51, Ser-54 to Trp-62, Gly-69 to Trp-77.	Pro-10 to Arg-15.
	5 1997	1998
	45 - 485	389 - 745
	592	593
	859769	859792
	HTPDM61	HTFOH87
	282	583

	96-116
0783: 10255: 10123: 0763: 0777:	3, 1, 1, 1, 3779: ,0755: 0662:
L0773: 2, L0775: 2, L0783: 2, L0809: 2, H0657: 1, H0241: 1, H0254: 1, H0255: 1, S0360: 1, H0208: 1, H0550: 1, H0673: 1, H0412: 1, H0413: 1, L0768: 1, L0794: 1, L0768: 1, L0665: 1, H0691: 1, H0690: 1, S0378: 1, H06521: 1, L0750: 1, L0750: 1, L0759: 1, S0436: 1, L0366: 1, S0242: 1 and S0424: 1.	AR096: 3, AR052: 3, AR053: 2, AR089: 2, AR03: 1, AR061: 1, AR060: 1, AR055: 1, AR104: 1, AR039: 0 L0745: 7, H0486: 4, L0764: 3, L0774: 3, L0779: 3, H0543: 3, H0130: 2, L0768: 2, L0766: 2, L0803: 2, L0542: 2, H0666: 2, H0672: 2, L0746: 2, L0755: 2, L0758: 2, L0596: 2, T0049: 1, H0657: 1, H0662: 1, S0358: 1, S0360: 1, H0580: 1, S0046: 1, S0222: 1, H0586: 1, H0013: 1,
	Leu-10 to Ser-20, Ala-49 to Gly-55, Ala-69 to Ala-74.
	6661
	284 - 760
	594
	859796
	IIWBDQ32
	584

L0021: 1, H0251: 1, H0266: 1, S0003: 1, S0214: 1, H0428: 1, H0644: 1, H0674: 1, H0674: 1, H0674: 1, H0674: 1, H0679: 1, H0616: 1, H0268: 1, H0679: 1, L0371: 1, L0770: 1, L0375: 1, L0372: 1, L0562: 1, L0550: 1, L0775: 1, L0375: 1, L0526: 1, L0529: 1, L0675: 1, H0670: 1, H0539: 1, L0740: 1, L0754: 1, L0759: 1, L0759: 1, L0759: 1, L0750: 1, L0759: 1, H0445: 1 and L0603: 1, L076: 3, AR053: 5, AR053: 6, AR104: 6, AR089: 6, AR053: 6, L0776: 8, L0776: 4, H0648: 4, L0759: 4, H0355: 3, H0648: 4, L0759: 4, H0355: 3, L0519: 3, H0684: 3, L0519: 3, H0684: 3, L0519: 3, H0684: 3, L0519: 3, H0684: 4, L0759: 4, H0355: 3, L0519: 3, H0684: 4, L0759: 4, H0355: 4, L0759: 4, L075	L0748: 3, L0747: 3, L0757:
Arg-7 to Ala-14, Phe-113 to Arg-118, Pro-124 to His-129, Glu-145 to Ala-153.	
199 - 2000	
595 199 660 660	
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3: 2, 4: H0392: 7: 2, 5: S0152: 5: S0436: 4: 1,	1, H0295: F: 1, 1, H0484: 5: 1, H0637: 1, H0497:	5: 1, , \$0474: 5: 1, 1, H0606: 5: 1, 1, H0413: :: 1, 1, L0770:	, L5564: : 1, , L0659: : 1, !, I10659: : 1, ; 2,
3, H0449: 2, S0358: 2, S0376: 2, S0444: 2, H0392: 2, T0006: 2, H0477: 2, L0775: 2, L0806: 2, S0152: 2, H0436: 2, L0758: 2, S0436: 2, H0423: 2, H0624: 1,	H0556: 1, H0157: 1, H0295: 1, H0294: 1, S0114: 1, H0657: 1, H0656: 1, H0484: 1, H0483: 1, S0356: 1, S0360: 1, S0408: 1, H0637: 1, S0007: 1, S0045: 1, H0497: H0391: 1, H0586: 1, H0497:	1, H0331: 1, H0485: 1, T0109: 1, T0048: 1, S0474: 1, L0040: 1, H0046: 1, S0051: 1, H0083: 1, H0606: 1, H0169: 1, H0316: 1, H0268: 1, H0412: 1, H0413: 1, T0042: 1, S0464: 1, H0633: 1, L0763: 1, L0770: 1, L0769: 1, L0638: 1,	L0771: 1, L0648: 1, L5564: 1, L0381: 1, L0774: 1, L0378: 1, L0655: 1, L0659: 1, L0809: 1, L0788: 1, L0532: 1, H0682: 1, H0659: 1, S0328: 1, S0380: 1, S0350: 1, H0696: 1, S0406:
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HNHMCO8 859848 596 10- 2001		383-406, 124-149, 8-35, 281- 302, 349- 368, 151- 171, 85- 104, 44- 62, 227- 245, 324- 340, 29- 45, 189- 205	65-84, 302-318, 571-587, 130-146, 366-382, 492-508
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HNHMC08 859848 596 10 - 2001 HNHMC08 859848 596 10 - 2001 HDPFH27 859875 597 95 - 2002 Ser 27 to Pro 35, Pro-106 to Lys-112, A Glu-119 to Ser-130, A Ser-182 to Val-187, A Lys-194 to Tyr-204, Lys-295 to Val-300, Lys-384 to Glu-390, Thr-512 to Thr-526, Ser-530 to Glu-537, Glin-556 to Lys-562, Lys-593 to Leu-601.			Xq25-q26
HNHMC08 859848 596 10 - 2001 HDPFH27 859875 597 95 - 2002 Ser 27 to Pro 35, Thr-87 to Ile-99, Pro-106 to Lys-112, Glu-119 to Ser-130, Ser-182 to Val-187, Lys-194 to Tyr-204, Lys-295 to Val-300, Lys-384 to Glu-390, Thr-512 to Thr-526, Ser-530 to Glu-537, Glin-556 to Lys-562, Lys-593 to Leu-601.	1, H0478: 1, H0479: 1, L0753: 1, S0434: 1, S0394: 1, L0592: 1, L0608: 1, H0668: 1, S0026: 1 and H0422: 1.	AR055: 3, AR053: 2, AR060: 2, AR033: 2, AR061: 1, AR052: 1, AR096: 1, AR089: 1, AR104: 0, AR039: 0 S0278: 2, S0218: 1, S0045: 1 and S0216: 1.	20, AR039: 13, AR033: 10, AR052: 8, AR096: 7, AR061: 2
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HNHMC08 859848 596 HDPFH27 859875 597		2001	2002
HNHMC08 859848 HDPFH27 859875		10 - 1251	95 - 1933
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	17q22-q24																				
		AR055: AR089:	Arg-200 to Ser-205, AR053: 1, AR096: 0, Pro-223 to His-229, AR039: 0, AR104: 0	H0144					-		-										
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	71-88	51-68, 4- 21
230200, 249000, 253250, 600525, 601844		
	AR089: 15, AR096: 15, AR052: 14, AR053: 12, AR060: 12, AR055: 11, AR104: 11, AR039: 10, AR033: 9, AR061: 6 H0171: 2, H0624: 1, S0222: 1, H0271: 1, S0390: 1, S0028: 1, L0786: 1 and S0031: 1.	AR039: 9, AR096: 8, AR053: 8, AR089: 7, AR052: 6, AR033: 5, AR055: 4, AR104: 4, AR060: 4, AR061: 2 L0766: 6, L0770: 3, H0632: 2, H0013: 2, L0483: 2, L0775: 2, L0663: 2, H0521: 2, L0759: 2, L0362: 2, S0354: 1, S0358: 1, H0486: 1, H0003: 1, H0318: 1, H0544: 1, H0457: 1, H0510: 1, H0428: 1, L0371: 1, L0521: 1, L0512: 1,
	Thr 26 to Lys-32, Asn-98 to Pro-105, Arg-133 to Thr-139.	Thr-33 to Thr-40, Lys-86 to Lys-103.
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